Remarks

Claims 21-50 were initially pending in the subject application. By way of the amendment in this response, claims 21 and 32 have been amended, claims 51 and 52 have been added, and claims 22 and 26 have been canceled. Applicants acknowledge that claims 35-50 stand withdrawn from consideration as being directed to a non-elected invention. Support for the amendments made to the claims can be found throughout the as-filed application (see, for example, original claims 11-12 and page 21, line 15 through page 22, line 24). Favorable consideration of the claims now presented, in view of the remarks and amendments set forth herein, is earnestly solicited.

Applicants wish to thank Examiner Ford for the courtesy of the telephonic interview conducted on March 3, 2006 with the undersigned. The remarks set forth in the Interview Summary Form that accompanied the instant Action are consistent with the substance of that interview. Applicants confirm that the election of species is phosphohalohydrins, specifically BrHPP, for prosecution.

Claims 21-34 have been rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. Specifically, the Office Action argues that the specification fails to provide sufficient description of a representative number of "synthetic activator compounds" of gamma delta T lymphocytes. Applicants respectfully traverse.

Applicants respectfully submit that claims 21-35 and new claims 51 and 52 comply with the written description element of 35 U.S.C. § 112, first paragraph. Applicants respectfully submit that the as-filed specification discloses a number of synthetic activators of gamma delta T-lymphocytes at pages 8 through 10 of the as-filed specification. For example, various phosphohalohydrin, phosphoepoxide, pyrophosphate, biphosphonate or bisphosphonate compounds are disclosed within the specification as being suitable synthetic activators of gamma delta T-lymphocytes. The specification also provides various references teaching how one skilled in the art is to make these compounds. Accordingly, Applicants respectfully submit that the as-filed specification provides adequate written description of the recited compounds that are activators of gamma delta T lymphocytes and reconsideration and withdrawal of the rejection is respectfully requested.

With respect to the issue raised regarding to the cytokine to be used in the practice of the claimed invention, Applicants disagree with the Examiner's position in this regard. However, in an

effort to advance prosecution in this matter, Applicants have amended the claims to recite IL-2 or IL-15 and respectfully submit that this aspect of the rejection is now moot. Applicants, however, retain the right to file a continuation application in this matter to pursue broader claims directed to other cytokines that would be useful in the proliferation of gamma delta T lymphocytes.

Claims 21-34 have been rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the enablement requirement. The Office Action argues that the as-filed specification fails to enable one skilled in the art to isolate gamma delta T lymphocytes from a biological preparation other than a blood sample. Applicants respectfully submit that this issue is now moot in view of the amendments made to the claims and respectfully request withdrawal of the rejection.

Claims 21-34 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Belmant *et al.* in view of Garcia *et al.* and Valeri *et al.* Claims 21-34 are also rejected under 35 U.S.C. § 103(a) as being unpatentable over Espinosa *et al.* in view of Garcia *et al.* and Valerie *et al.* The Office Action argues that the claimed methods of producing gamma delta T lymphocyte populations are obvious over the combination of the cited references as the primary references teach the activation of gamma delta T lymphocytes using BrHpp in conjunction with IL-2. Garcia *et al.* is relied upon for the teaching of IL-15 as an activator of gamma delta T lymphocyte proliferation and Valerie *et al.* is relied upon for a teaching of cytapheresis and the freezing of cell samples. Applicants respectfully traverse the rejections.

Applicants respectfully submit that the claims are not obvious over the combination of Belmant *et al.* or Espinosa *et al.* in view of Garcia *et al.* and Valeri *et al.* While obviousness is ultimately a legal determination, it is based on several underlying issues of fact, namely: (1) the scope and content of the prior art; (2) the level of skill of a person of ordinary skill in the art; (3) the differences between the claimed invention and the teachings of the prior art; and (4) the extent of any objective indicia of non-obviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). When obviousness is based on the teachings of multiple prior art references, there must also be some "suggestion, teaching, or motivation" that would have led a person of ordinary skill in the art to combine the relevant prior art teachings in the manner claimed. *See Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1359-60 (Fed.Cir.1999); *Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1572 (Fed.Cir.1996). "The reason, suggestion, or motivation to combine [prior

art references] may be found explicitly or implicitly: 1) in the prior art references themselves; 2) in the knowledge of those of ordinary skill in the art that certain references, or disclosures in those references, are of special interest or importance in the field; or 3) from the nature of the problem to be solved, 'leading inventors to look to references relating to possible solutions to that problem.' " *Ruiz v. A.B. Chance Co.,* 234 F.3d 654, 665 (Fed.Cir.2000) (quoting *Pro-Mold,* 75 F.3d at 1572). Additionally, and as the Patent Office is aware, all the claim limitations must be taught or suggested by the prior art in order to establish the *prima facie* obviousness of a claimed invention. *In re Royka,* 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974).

In the case of the instantly claimed invention, it is respectfully submitted that the combination of references fails to teach each of the limitations of the claims, particularly maintaining the cells undergoing culture at a density less than about 5 x 10^6 cells/ml during said culturing step. With respect to this limitation, the Patent Office fails to provide any reference or evidence teaching why one skilled in the relevant art would wish to maintain such a cell density during culture; rather, the Office Action simply asserts that maintaining cells at such a concentration would be within the purview of one of ordinary skill in the art to initiate and maintain the culture at appropriate cell concentrations for the needs of the culture. Applicants respectfully submit that more is required than a simple assertion to this effect and that the *prima facie* obviousness of the claimed invention has not been established by the Patent Office.

Even assuming, *arguendo*, that a *prima facie* case of obviousness has been established for the claimed invention, Applicants respectfully submit that the presently claimed method produces unexpected results as compared to methods similar to those of Espinosa *et al.* and Belmant *et al.* For example, culture of biological preparations as defined and according to the claimed methods where the cell density was maintained at less than about 5 x 10^6 cells/ml during the culturing step resulted in the generation of cell preparations containing greater than about 90% gamma delta T lymphocytes after 10 days of culture, greater than about 95% gamma delta T lymphocytes after about 15 days of culture and about 95% gamma delta T lymphocytes after 21 days of culture (see paragraph bridging pages 25-26 and Table 8). These results were reproducible and consistent across multiple samples. In contrast, when protocols similar to those of Espinosa *et al.* and Belmant *et al.* were followed and cells were cultured in 24 well plates as taught in Espinosa *et al.*, a far more variable yield of gamma

delta T lymphocytes was observed. Accordingly, it is respectfully submitted that the claimed method is not obvious over the teachings of the cited references as it produces unexpected results as compared to the results from following a protocol substantially similar to that of Belmant *et al.* or Espinosa *et al.*; namely, the claimed method reproducibly produces gamma delta T lymphocyte populations that contain significantly more gamma delta T lymphocytes as compared to the cited prior art methods. In view of such unexpected results, reconsideration and withdrawal of the rejections is respectfully requested.

Claims 21 and 32 have been provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 80 and 100 of copending application 10/537,394. The Office Action argues that the difference between the current claims and those of the '394 application is the in vitro culture of cells as compared to the in vivo stimulation of gamma delta T lymphocytes. Applicants respectfully submit that the claims are not obvious over the claims of the '394 application.

A double patenting rejection of the obviousness-type is "analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. 103" except that the patent principally underlying the double patenting rejection is not considered prior art. *In re Braithwaite*, 379 F.2d 594, 154 U.S.P.Q. 29 (C.C.P.A. 1967). Therefore, any analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination. *In re Braat*, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887, 225 U.S.P.Q. 645 (Fed. Cir. 1985). Accordingly, the analysis employed in an obviousness-type double patenting determination parallels the guidelines for a 35 U.S.C. 103(a) rejection and the factual inquiries set forth in *Graham v. John Deere Co.,* 383 U.S. 1, 148 U.S.P.Q. 459 (1966) are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are employed when making an obviousness-type double patenting analysis. Further, any obviousness-type double patenting rejection should make clear the differences between the inventions defined by the conflicting claims and the reasons why a person of ordinary skill in the art would conclude that the invention defined in the claims of the pending application at issue would have been an obvious variation of the invention defined in a claim in the patent. Finally, and as discussed above, all the claim limitations must be

taught or suggested by the prior art in order to establish the *prima facie* obviousness of a claimed invention,. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974).

Against this background, Applicants respectfully submit that the currently claimed invention is not obvious over the claims of the claims of the '394 application. For example, the claims of the '394 application are silent with respect to maintaining the cells at a density less than about 5×10^6 cells/ml during the culturing step. Additionally, the reference fails to teach or recite, within the claims, biological samples such as a blood sample or a cytapheresis sample. Accordingly, Applicants respectfully that the Patent Office has failed to establish that the claims of this application are obvious variants of the '394 application and reconsideration and withdrawal of the rejection is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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